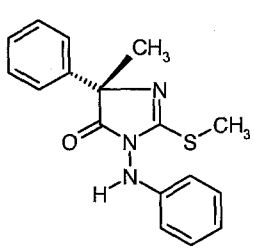
Data Evaluation Report on the phototransformation of fenamidone in water (Direct Photolysis in Water)

PMRA Submission Number {.....} EPA MRID Number 45385830

Data Requirement: PMRA Data Code:
EPA DP Barcode: D275213
OECD Data Point:
EPA Guideline: 161-2

Test material:
Common name: Fenamidone
Chemical name
IUPAC: (+)-(4*S*)-4-Methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one.
CAS Name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (*S*)-.
CAS Registry No: 161326-34-7.
Synonyms: Reason 500 SC Fungicide.
Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one.
(*S*)-1-Anilino-4-methyl-2-methylthio-4-phenylimidazolin-5-one.
(*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one.
Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (5*S*)-.
(5*S*)-3,5-Dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-4*H*-imidazol-4-one.
RPA407213.
SMILES string:

Chemical Structure:



Primary Reviewer: Lynne Binari
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Date: 26 August, 2002

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Company Code: [for PMRA]
Active Code: [for PMRA]
Use Site Category: [for PMRA]
EPA PC Code: 046679

CITATION: Corgier, M.M. and A.P. Plewa. 1998. ^{14}C-RPA407213 photodegradation in water. Unpublished study performed by Rhône-Poulenc Agro, Lyon, France, and sponsored by Aventis CropScience, Research Triangle Park, NC (pp. 1, 2). Laboratory Study Number 96-127. Report Reference R&D/CRLD/AN/9716602. Study initiated November 4, 1996 and completed January 28, 1998 (pp. 1, 5).

Aventis's response to USEPA's review of the Reduced Risk Document (October 12th, 2001).

Regulatory Conclusions: This study, conducted with [C-phenyl-U-^{14}C]-labeled fenamidone, is classified acceptable and partially satisfies Subdivision N Guideline §161-2 data requirements. This study plus the aqueous photolysis study conducted with [N-phenyl-U-^{14}C]-labeled fenamidone (MRID 45385831) fully satisfy Subdivision N Guideline §161-2.

Scientific Conclusions: Direct photolysis is water is an important degradative pathway for fenamidone in the environment. In pH 7 buffered solution, the **phototransformation half-life** is 25.5 hours based on the continuous radiation used in the study, or 51 hours based on a 12 hour light/12 hour dark cycle.A predicted **environmental phototransformation half-life** for fenamidone, derived from the in-laboratory measured half-life under artificial light conditions, was calculated as 5.0 days (k= -0.138 day^{-1}) for cloudless summer sunlight at 20-50°N latitude (Florida). Fenamidone is hydrolytically stable in pH 7 buffered solution. Two photoproducts were found at greater than 10% of the applied radioactivity.

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PMRA Submission Number {.....} EPA MRID Number 45385830

EXECUTIVE SUMMARY

The aqueous phototransformation of [C-phenyl-U-^{14}C]-labeled (+)-(4*S*)-4-methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one (fenamidone, RPA407213) was studied at 25 ± 1°C in sterile aqueous 0.02 M phosphate buffer at pH 7 at a nominal concentration of 3.9 mg a.i./L under continuous irradiation using a UV-filtered xenon arc lamp (300-800 nm, light intensity 720 W/m^2) for 48 hours. It was calculated that 1 hour of xenon arc lamp irradiation was equivalent to 0.195 days of cloudless summer sunlight at 20-50°N latitude. This experiment was conducted in accordance with USEPA Subdivision N Guideline §161-2 and in compliance with USEPA GLP Standards (40 CFR, Part 160, 1989). Each irradiated test system consisted of a double-walled Pyrex photoreactor vessel sealed with a silica glass disc and equipped with inlet/out ports to allow for collection of CO_2 and organic volatiles at each sampling interval. Dark control solutions were contained in a sealed borosilicate glass bottle with a UV-absorbing jacket and maintained at 25 ± 1°C in darkness in an incubator. The treated test solution was sampled at time 0, duplicate irradiated irradiated solutions were taken after 15, 24, 31, 39 and 48 hours, and dark control solutions were taken at 48 hours. Test solutions were analysed directly by reverse-phase HPLC; identifications of fenamidone and transformation products was done by co-chromatography with unlabeled reference standards. Identifications of [^{14}C]compounds were confirmed using LC/MS with atmospheric pressure chemical ionization.

After 48 hours of incubation, mean material balances (n = 2) had declined from an initial 102.3 ± 0.06% of the applied radioactivity to 93.7 ± 0.81% in irradiated solutions and were 101.9 ± 0.46% in dark control solutions. No transformation of [C-phenyl-U-^{14}C]fenamidone occurred in the dark control solutions with fenamidone comprising 100.1 ± 0.45% of the applied at 48 hours posttreatment.

In irradiated solutions, [C-phenyl-^{14}C]fenamidone decreased from 101.0 ± 0.0% of the applied at time 0 to 87.5 ± 0.15% at 24 hours and was 27.9 ± 0.8% at 48 hours. The major transformation products in irradiated solutions were RPA408056 (4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one) detected at a maximum 37.1% of the applied and RPA405862/RPA410193 (4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione/(S)-4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione) detected at a maximum 13.6% after 48 hours. Minor transformation products included RPA418915 [Photo-H; (*S*)-5-methyl-2-methylthio-3-[(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one] detected at a maximum 5.7% at 48 hours plus eleven unidentified [^{14}C]compounds each detected at ≤3.7% of the applied. In irradiated solutions, evolved $^{14}CO_2$ totaled <1% of the applied at the final sampling interval and organic volatiles were ≤0.1% at any sampling interval.

The **half-life** value of [C-phenyl-U-^{14}C]fenamidone, based on first-order kinetics and linear regression, was 25.5 hours (r^2 = 0.810) in the irradiated pH 7 solution based on the continuous

irradiation conditions used in the study. As the reaction rate followed first order kinetics, the half-life and the DT50 are equivalent.

The **phototransformation half-life** is 25.5 hours based on the continuous radiation used in the study, or 51 hours based on a 12 hour light/12 hour dark cycle.

A predicted **environmental phototransformation half-life** for fenamidone, derived from the in-laboratory measured half-life under artificial light conditions, was calculated as 5.0 days (k= -0.138 day^{-1}) for cloudless summer sunlight at 20-50°N latitude.

A phototransformation pathway proposed by the registrant included fenamidone degrading primarily to RPA408056 (a cleavage product containing the "phenyl-imidazolinone" moiety), but also to RPA405862/RPA410193 and methyl mercaptan (CH_3SH) via photoinduced hydrolysis to release the methylthio group and to RPA418915 (Photo H).

Results Synopsis:

Test medium: 0.02 M phosphate buffer at pH 7.
Source of irradiation: Xenon arc lamp.
Half-life (DT50) value: 25.5 hours ($r^2 = 0.810$).

Major transformation products: 4-Methyl-2-methylthio-4-phenyl-2-imidazolin-5-one (RPA408056).
4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione (RPA405862; *S*- enantiomer RPA410193).

Minor transformation products: (*S*)-5-methyl-2-methylthio-3-[(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one (RPA418915, Photo-H).
Eleven unidentified [^{14}C]compounds.

Study Acceptability: This study, conducted with [C-phenyl-U-^{14}C]-labeled fenamidone, is classified acceptable and partially satisfies Subdivision N Guideline §161-2 data requirements. This study plus the aqueous photolysis study conducted with [N-phenyl-U-^{14}C]-labeled fenamidone (MRID 45385831) fully satisfy Subdivision N Guideline §161-2.

Data Evaluation Report on the phototransformation of fenamidone in water (Direct Photolysis in Water)

PMRA Submission Number {.....} EPA MRID Number 45385830

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: This study was conducted in accordance with USEPA Subdivision N Guideline §161-2. No significant deviations were noted.

COMPLIANCE: This study was conducted in compliance with USEPA GLP Standards (40 CFR, Part 160, 1989) and OECD GLP in the Testing of Chemicals (Paris, 1982; p. 3). Signed and dated GLP, Data Confidentiality and Quality Assurance statements were provided (pp. 2-4). A Certification of Authenticity statement was not provided.

A. MATERIALS

1. Test Material: [C-phenyl-U-^{14}C]RPA407213 ("phenyl imidazolinone moiety")

Chemical Structure:

Description: Technical (p. 13).

Purity: Radiochemical purity: >98.0% (p. 13; Appendix A, pp. 51-55).
Batch No.: CFQ9085.
Analytical purity: Not provided.
Specific activity: 38 mCi/mM (1.41 Gbq/mM).
Location of the label: Uniformly labeled on the phenyl ring ("phenyl imidazolinone moiety")

99.8% *S*-enantiomer.

Storage conditions of test chemical: Not specified.

Table 1: Physico-chemical properties of fenamidone.

Parameter	Details	Comments
Solubility:	7.8 mg/L in water at 20°C. 86.1 g/L in acetonitrile at 20°C.	
Vapor pressure/volatility:	Not reported.	
UV absorption:	Absorption band tailing above 300 nm	In methanol:pH 7 buffer solution (90:10, v:v).
pK_a:	Not reported.	
K_{ow}	Not reported.	
Stability at room temperature:	Not reported.	

Data obtained from p. 13, Appendix B, p. 57 in the study report.

2. Buffer Solution: The pH 7 buffer solution was prepared using de-ionized water further purified using an Elgastat UHP apparatus (final resistivity > 18 MΩxcm, p. 14).

Table 2: Description of buffer solution.

pH	Type of buffer and final molarity	Composition
7	0.02 M phosphate	2.72 g KH_2PO_4 was dissolved in 950 mL water, the pH was adjusted to 7 with 1 N NaOH, then brought to final volume of 1000 mL with water.

Data obtained from p. 14, Table II, p. 37 in the study report.

3. Details of light source:

Table 3: Artificial light source.

Property	Details
Type of lamp used:	Xenon arc lamp, Heraeus Suntest.
Emission wavelength spectrum:	300-800 nm.
Light intensity:	720 W/m^2, measured with a calibrated Radialux global detector (300-800 nm) at equivalent distance from light source as surface of test solutions.
Filters used:	UV filter eliminated radiation <290 nm.
Relationship to natural sunlight:	1 hour of xenon arc lamp irradiation determined to be equal to 0.195 days of cloudless sunlight irradiation in summer at 20-50°N latitude.

Data obtained from pp. 14, 17-19; Appendix C, pp. 59, 60, in the study report.

B. EXPERIMENTAL CONDITIONS:

1. Preliminary experiments: None.

2. Experimental conditions:

Table 4: Experimental design.

Parameter		Details
Duration of the test:		48 hours.
Application rate: Nominal Measured		3.9 mg a.i./L. 3.77 mg a.i./L (mean).
Dark controls used (Yes/No):		Yes.
Replications	Dark controls:	Duplicate.
	Irradiated:	Duplicate.
Preparation of the test medium:	Volume used/treatment:	99 mL of sterile pH 7 buffer solution treated with 1.0 mL of 390 mg a.i./L [C-phenyl-^{14}C]fenamidone in acetonitrile.
	Method of sterilization:	Prior to use, all glassware, the photoreactor vessels and pH 7 buffer solution were autoclave-sterilized at 121°C for 35 minutes.
	Co-solvent, if any:	Acetonitrile; final concentration of 1% (v:v).
Test apparatus (Type/material/ volume):	Dark controls:	Borosilicate glass bottles (100-mL), with UV-absorbing jackets and sealed with screw caps, containing the treated test solution were maintained at 25 ± 1°C in darkness in an incubator.

Parameter		Details
	Irradiated:	Double-walled Pyrex photoreactor vessels (100-mL, i.d. 5.2 cm), equipped with inlet/outlet ports, containing treated test solution were capped with silica glass discs. Water maintained at 25 ± 1°C with a cryothermostat was circulated through the double-wall of each vessel. Each photoreactor vessel contained a stirring bar and was placed on a Multipost magnetic stirrer in the Suntest apparatus; it was not specified if the test solutions were stirred continuously.
Details of traps for CO_2 and organic volatiles, if any:	Dark controls:	None.
	Irradiated:	At each sampling interval after time 0, filtered (0.2 µm) air was drawn (flow rate not specified) through the vessel then sequentially through traps containing ethylene glycol monomethyl ether (Methyl Cellosolve®; one trap) and 2 N NaOH (two traps).
If no traps were used, is the system closed/open?		Dark control systems were closed; no volatiles collection. Irradiated systems were closed, but volatiles were collected at each sampling interval.
Any indication of the test material adsorbing to the walls of the test apparatus?		Not indicated.
Experimental conditions.	Temperature (°C):	25 ± 1°C. For irradiated and dark controls, a vessel containing pH 7 buffer solution and incubated alongside the test samples was linked to a temperature recorder; temperature recorded hourly.
	Duration of light/darkness:	Continuous irradiation.
Other details, if any:		None.

Data obtained from pp. 14-17, 20, Figures 1-2, pp. 32-33, Table II, p. 38, Appendix C3, p. 61 in the study report.

3. Supplementary experiments: The following supplemental experiments were conducted:

Sterility determinations. Triplicate aliquots (25 µL) of irradiated (31- and 48-hour samples) and dark control (48-hour) solutions were applied to screw-capped bottles (60-mL) containing autoclave-sterilized (121°C for 35 minutes) nutrient solution (pH 7.2) consisting of 0.01 mg/L D(+) glucose, 0.005 mg/L yeast extract and 0.005 mg/L Bacto-peptone (pp. 20, 21). The treated nutrient solutions were incubated 3.9-4.7 days with orbital stirring at an average temperature of 30.1°C (range 30.0-30.3°C). Following incubation, the solutions were assessed visually (clear/cloudy) and optical density was determined by measuring absorbance at 500 nm.

Stability of fenamidone and its transformation products in test solution. Duplicate aliquots of the 48-hour irradiated solution (replicate B) were re-analyzed by HPLC as described below after 54 days of frozen (*ca.* -20°C) storage (p. 28, Table XIV, p. 49).

4. Sampling:

Table 5: Sampling details.

Parameters	Details
Sampling intervals:	Time 0. Irradiated solutions at 15, 24, 31, 39 and 48 hours. Dark controls at 48 hours.
Sampling method:	Entire sample collected.
Method of collection of volatile compounds, if any:	Volatiles collected from irradiated photoreactor vessels at each sampling interval after time 0.
Sampling intervals/times for: sterility check: pH measurement:	 Irradiated solutions at 31 and 48 hours. Dark controls at 48 hours. Each sampling interval.
Sample storage before analysis:	Aliquots of the test solutions were taken for LSC and HPLC analyses upon sampling, with remaining solution placed in frozen (ca. -20°C) storage.
Other observations, if any:	None

Data obtained from pp. 16, 20 of the study report.

C. ANALYTICAL METHODS:

Extraction/clean up/concentration methods, if used: Samples were analyzed as collected, without manipulation or modification.

Volatile residue determination: Aliquots of the volatiles trapping solutions were analyzed for total radioactivity by LSC (p. 21).

Total ^{14}C measurement: Duplicate aliquots (5 mL) of the irradiated and dark control test solutions were analyzed for total radioactivity by LSC (p. 21).

Derivatization method, if used: A derivatization method was not employed.

Identification and quantification of parent compound: Aliquots of the test solutions were analyzed by reverse-phase HPLC under the following conditions: C-18 Alltima column (4.6 x 250 mm, 5 µm particle size), isocratic mobile phase of acetonitrile:0.1% aqueous trifluoroacetic acid (45:55, v:v), injection volume 25-50 µL, flow rate 1.0 mL/minute, UV (230 nm) and radioactivity detection (p. 22). For identification of parent fenamidone, [^{14}C]-labeled and unlabeled fenamidone were chromatographed concurrently with test solutions. Identifications of parent fenamidone were confirmed by LC/MS with atmospheric pressure chemical ionization (APCI; Appendix F, pp. 103, 104, 106, 109-117). LC conditions were as described above, except injection volume was 50-100 µL (Appendix F, pp. 108, 119). MS conditions were as follows: Micromass Quattro II Triple Quadripole MS, source type pepperpot APCI, drying gas nitrgen at 400 L/hour, sheath gas nitrogen at 75-100 L/hour, source temperature 150°C, APCI probe temperature 400°C, ion energy 2.0 V, scan range 100-800 a.m.u. (Appendix F, pp. 99, 100, 120).

Identification and quantification of transformation products: Transformation products were isolated and quantified by HPLC and LC/MS as described for the parent compound and identified by comparison to reference (Appendix E, pp. 82-86; Appendix F, pp. 103, 104, 106, 109-117).

Detection limits (LOD, LOQ) for the parent compound: The limit of detection for HPLC analyses was 0.3% of the applied radioactivity equivalent to 0.57 ng (p. 27).

Detection limits (LOD, LOQ) for the transformation products: Detection limits were the same as for fenamidone.

II. RESULTS AND DISCUSSION:

A. TEST CONDITIONS: The temperature (24.1-25.6 °C and 24.6-25.3 °C for irradiated and dark control solutions, respectively), pH (7.03-7.12 and 7.07 for irradiated and dark control solutions, respectively), sterility and other experimental conditions were maintained throughout the study (p. 25, Tables I-II, pp. 36- 37, Table IV, p. 39).

B. MATERIAL BALANCE: After 48 hours of incubation, mean (n = 2) total recovery of radiolabeled material had decreased from an initial 102.3 ± 0.06% (range 102.28-102.40%) of the applied to 93.71 ± 0.81% (92.90-94.52%) in irradiated solutions and was 101.9 ± 0.46% (101.40-102.32%) in dark control solutions Table VI, p. 41).

Table 6: Phototransformation of [C-phenyl-U-^{14}C]fenamidone in pH 7 buffer solution expressed as percentage of applied radioactivity (mean ± s.d., n = 2).

Compound and/or code		Sampling times (hours)					
		0	15	24	31	39	48
Fenamidone (RPA407213)	irradiated	101.0 ± 0.0	92.0 ± 0.95	87.5 ± 0.15	61.1± 13.0	43.7 ± 5.7	27.9 ± 0.80
	dark		NA[1]	NA	NA	NA	100.1 ± 0.45
RPA408056	irradiated	0.9 ± 0.2	3.8 ± 0.95	6.6 ± 0.5	20.7± 7.05	28.7 ± 2.25	35.6 ± 1.5
	dark		NA	NA	NA	NA	0.9 ± 0.1
RPA405862 (*S*- enantiomer, RPA410193)	irradiated	0.4 ± 0.2	1.8 ± 0.15	2.2 ± 0.05	6.9 ± 3.1	9.3 ± 1.4	13.4 ± 0.25
	dark		NA	NA	NA	NA	0.6 ± 0.1
RPA418915 (Photo-H)	irradiated	<LOD[2]	0.3 ± 0.1	1.0 ± 0.0	3.5 ± 1.3	4.5 ± 0.7	5.5 ± 0.2
	dark		NA	NA	NA	NA	<LOD
Total Unidentified Others[3]: (# of cmpds with each ≤3.7% of applied)	irradiated	0.04 ± 0.1 (0)	1.66 ± 0.1 (6)	2.44 ± 0.35 (8)	5.7 ± 2.6 (8)	9.44 ± 1.2 (9)	11.3 ± 1.4 (10)
	dark		NA	NA	NA	NA	0.31 ± 0.2 (1)
CO_2[4]	irradiated	NA	ND[4]	0.01 ± 0.0	0.02 ± .01	0.05 ± 0.01	0.08 ± 0.0
Organic volatiles:	irradiated	NA	ND	0.01 ± 0.0	0.005 ± 0.005	ND	0.005 ± 0.005
Total % recovery:	irradiated	102.3 ± 0.06	99.4 ± 0.36	99.7 ± 0.05	97.9 ± 1.05	95.6 ± 0.12	93.7 ± 0.81
	dark		NA	NA	NA	NA	101.9 ± 0.46

[1]NA = Not analyzed.
[2]LOD = Limit of detection for HPLC reported as 0.3% of applied radioactivity (p. 27).
[3]Determined by Dynamac reviewer.
[4]Volatilized radioactivity was not determined for dark controls because none was expected.
[4]ND = Not detected; limit of detection for LSC analyses not reported.
Data obtained from Tables VI-XIII, pp. 42-48; Appendix D, pp. 73-79, and Appendix E, pp. 83-85 of the study report. Means provided by registrant, standard deviations calculated by Dynamac reviewer.

C. TRANSFORMATION OF PARENT COMPOUND: No transformation of [C-phenyl-^{14}C]fenamidone occurred in dark control solutions with fenamidone comprising 100.1 ± 0.45% (100.5-99.6%) of the applied radioactivity at 48 hours posttreatment (Table XIII, p. 48).

In irradiated solutions, [C-phenyl-^{14}C]fenamidone decreased rapidly from a mean 101.0 ± 0.0% of the applied at time 0 to 61.1 ± 13.0% (48.1-74.1%) at 31 hours, 43.7 ± 5.7% (38.0-49.4%) at 39 hours and was 27.9 ± 0.8% (27.1-28.7%) at 48 hours (Figure 4, p. 35; Tables VII-XII, pp. 42-47).

HALF-LIFE: The half-life for fenamidone in the irradiated buffer solution was determined by the reviewer to be 25.5 hours using linear regression analysis based on first-order kinetics as calculated by Corel Quattro Pro 8 software. This value is similar to that reported by the study author (25.7 hours, $r^2 = 0.847$), who used Excel v. 4 software (p. 28).

Half-lives*

Test system	First order linear			DT50* (days)	DT90 (days)
	Half-life (hours)	Regression equation	r^2		
Irradiated	25.5 hours	Linear form y = mx + b as $lnC = -kt + lnC_0$; lnC_0 is initial concentration (b = y intercept), lnC is concentration at time t (y), k is the slope (m), t is time (x) or $kt = lnC_0 - lnC$. Half-life ($t_{1/2}$) = -(ln 2/k).	0.810	25.5 hours	ND
Dark	Stable		ND	Stable	ND

*Half-lives calculated by the reviewer using data obtained from Tables VII-XIII, pp. 42-48 of study report. Values identified as DT50s are in fact equivalent to half-lives calculated using first order liner regression.
ND Not Determined

Since fenamidone was stable in the dark control, the half-life for phototransformation is equivalent to half-life observed in the irradiated samples. The phototransformation half-life is 25.5 hours based on the continuous radiation used in the study, or 51 hours based on a 12 hour light/12 hour dark cycle.

The predicted environmental phototransformation half-life, derived from the in-laboratory measured half-life under artificial light conditions, was calculated as 5.0 days ($k = -0.138$ day $^{-1}$) cloudless summer sunlight at 20-50°N latitude (p. 28).

TRANSFORMATION PRODUCTS

Table 7: Chemical names for identified transformation products of fenamidone

Applicant's Code Name	CAS Registry Number	Chemical Name(s)	Chemical formula	Molecular weight (g/mol)	Smiles string
RPA408056		IUPAC: 4-Methyl-2-methylthio-4-phenyl-2-imidazolin-5-one IUPAC: 5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one CAS: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-		220.3	
RPA405862	161326-62-1	IUPAC: 4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione IUPAC: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione CAS: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-		281.3	
RPA410193		IUPAC: (*S*)-4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione; *S*-enantiomer of RPA405862		281.3	
RPA418915 (Photo-H)		IUPAC: (*S*)-5-Methyl-2-methylthio-3-[(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one		325.4	

The major transformation products in irradiated solutions were RPA408056 detected at a maximum 35.6 ± 1.5% (34.1-37.1%) of the applied and RPA405862 at 13.4 ± 0.25% (13.1-13.6%) after 48 hours (Figure 4, p. 35, Tables VIII-XII, pp. 42-47). Minor transformation products included RPA418915 (Photo-H) detected at a maximum 5.5 ± 0.2% (5.3-5.7%) at 48 hours and eleven unidentified [^{14}C]compounds each detected at ≤3.7% of the applied.

VOLATILIZATION: Evolution of $^{14}CO_2$ and organic [^{14}C]volatiles was not significant in irradiated solutions comprising only 0.09% and ≤0.01% of the applied, respectively, after 48 hours (Table V, p. 40).

TRANSFORMATION PATHWAY: A phototransformation pathway for the degradation of fenamidone in aqueous solution was proposed by the registrant (p. 30). In irradiated solutions, fenamidone degraded primarily to RPA408056 (4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one) via loss of the aniline ring, but also to 4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-

dione (RPA405862/RPA410193) via hydrolysis to release the methylthio group. Fenamidone also transforms to the photoproduct (*S*)-5-methyl-2-methylthio-3-[(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one (RPA418915, Photo-H), via hydrolysis of the aniline ring (pp. 19, 55 in MRID 45385831).

D. SUPPLEMENTARY EXPERIMENT-RESULTS: There was no apparent degradation of fenamidone and its transformation products in a 48-hour irradiated test solution (replicate B) following 54 days of frozen (*ca.* -20°C) storage (Table XIV, p. 49).

III. STUDY DEFICIENCIES: No deficiencies were identified. This study, conducted with [C-phenyl-U-^{14}C]-labeled fenamidone, can be used to partially satisfy Subdivision N Guideline §161-2 data requirements. This study plus the aqueous photolysis study conducted with [N-phenyl-^{14}C]-labeled fenamidone (MRID 45385830) fully satisfy Subdivision N Guideline §161-2.

IV. REVIEWER'S COMMENTS:

1. In the document *Reduced Risk Rationale for the Use of Fenamidone on Potatoes and Vegetables* (B0003264, no MRID), it is reported that fenamidone is the S-enantiomer compound with none of the R-enantiomer present (p. 16). It is further stated that analysis demonstrated that all of the metabolites of fenamidone that retain the imidazolinone ring are also pure S-enantiomers. No evidence was provided to support this statement. The registrant notes that the racemic mixture was often referenced in the original study reports.

   Therefore, although the study author identified Photolyte A as being a mixture of RPA405862 (4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione) and RPA410193 [(*S*)-4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione], where RPA410193 is the S-enantiomer of RPA405862, Photolyte A in fact consists only of RPA410193. To remain consistent with the study report, the term RPA405862/RPA410193 is used throughout this DER.

2. The registrant's code numbers used in this MRID do not match the code numbers presented in the *Reduced Risk Rationale for the Use of Fenamidone on Potatoes and Vegetables* (B0003264, no MRID). For example, RPA405862/RPA410193 is RPA410193, RPA409344 is RPA413350, and RPA408056 is RPA412708. The reason for the different code numbers was not discussed. Using the conversion of RPA405862/RPA410193 to RPA410193 and the chemical names provided with the studies as a guide, it appears that in the studies, the registrant's code numbers are for the R-enantiomer form or the racemic mixture. In the

Reduced Risk petition, the registrant states that only the S-enantiomer form of the parent and transformation products exist. Registrant's code RPA418915 (Photo-H) is unaffected because this is the code for the *S*-enantiomer.

3. Multiple IUPAC names were found for fenamidone and several of its transformation products. It could not be determined which name was currently preferred. All of the chemical names that were used in the MRIDs in this data package are included in the *Chemical names for identified transformation products* table in this DER and with the attached chemical structures.

4. In a hydrolysis study (MRID 45385829), fenamidone was found to hydrolyze at pH 4 and 9, but was relatively stable at pH 5 and 7. At 31 days posttreatment (final sampling interval), fenamidone comprised 91.15% of the applied radioactivity in pH 5 solutions and 95.34% in pH 7 solutions. No major degradates were identified; minor degradates were RPA405862/RPA410193 and RPA409344.

5. The registrant reported that there was no attempt to collect volatiles from the dark control solutions because no volatiles compounds were formed during the hydrolysis study (p. 12).

6. The r^2 value associated with the half-life is only 0.810. Considering the relatively small number of sampling points in the data set, this indicates that the fit of the regression line to the observed data is poor. The poor fit appears to result from variable data rather than changes in the rate of degradation with time.

7. For identification of parent fenamidone and its degradates, test solutions were reportedly chromatographed concurrently with [^{14}C]-labeled and unlabeled fenamidone and unlabeled reference standards of possible degradates (pp. 22, 82-86). However, neither chromatograms of unlabeled reference standards alone for retention time comparison nor chromatograms of test solutions co-chromatographed with unlabeled reference standards were provided.

8. It appears that the registrant calculated the reported photodegradation half-life for fenamidone of 25.7 hours (r^2 = 0.847) using mean values of fenamidone (percent of applied radioactivity) detected at each sampling interval (p. 34). It is preferred that individual replicate values are used for calculations to more accurately reflect the behavior of the compound. However, a similar photodegradation half-life for fenamidone (25.5 hours, r^2 = 0.810) was determined by the Dynamac reviewer using [^{14}C]fenamidone concentrations at all sampling intervals and least squares linear regression analysis assuming degradation followed first order kinetics as calculated by Corel Quattro Pro 8 software.

9. The unidentified [^{14}C]compound Photo-H in this study was also detected in the aqueous photolysis study conducted with [phenylamino-U-^{14}C]fenamidone and positively identified as (*S*)-5-methyl-2-methylthio-3-[(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one (RPA418915) by LC/MS-ACPI with comparison to a synthesized reference standard of RPA418915 (pp. 19, 55, 56, 76 in MRID 45385831).

10. Representative HPLC chromatograms presented on p. 73-79 indicated good separation of peaks.

11. The maximum proposed per season application rate is 1.07 lb a.i./A (equivalent to 0.54 mg a.i./kg or 0.60 kg a.i/ha).

V. REFERENCES: The following references were cited in the study:

1. Certon, A., J. Cousin and G. Turier. 1997. RPA407213 active ingredient-water and solvent solubility, part C. Rhône-Poulenc Agro Report Nr R&D/CRLD/AN/9715441, Study No. 96-79.

2. Corgier, M.M., G. Turier and A.P. Plewa. In progress. ^{14}C-RPA407213: hydrolysis at 25°C at pH 4, 5, 7 and 9. Rhône-Poulenc Agro Report Nr R&D/CRLD/AN/9716604, Study No. 96-108.

3. Judd, D.B., *et al.* 1974. Spectral distribution of typical daylight as a function of correlated color temperature. J. Optical Soc. Am., 58: 4.

4. Mill, T. *et al.* Laboratory protocols for evaluating the fate of organic chemicals in air and water. EPA-600/3-82-022. EPA contact 68-03-2227.

5. Parker, S. and J.P. Leahey. 1988. Development of a method to investigate the photodegradation of pesticides. Proc. Brighton Crop Prot. Conf. Pests and Diseases, pp. 663-668.

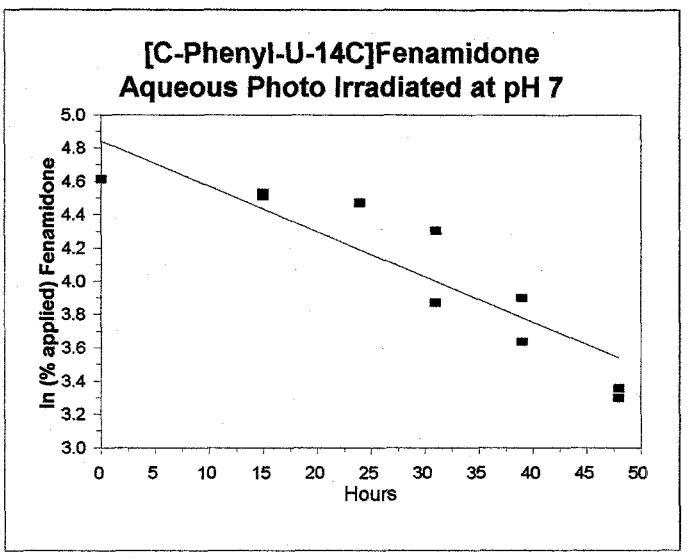
6. EPA: 40 CFR 158 Subdivision N, Environmental Fate Pesticide Assessment Guideline: §161-2.

Attachment 1

Quattro Pro Graphs and Spreadsheets

Fenamidone Photolysis in pH 7 Buffer Solution
MRID 45385830

Irradiated		
Half-life of C-Phenyl-U-^{14}C		
Fenamidone		
Hour	% AR	Ln(% AR)
0	101.0	4.615121
0	101.0	4.615121
15	92.9	4.531524
15	91.0	4.51086
24	87.3	4.46935
24	87.6	4.472781
31	74.1	4.305416
31	48.1	3.873282
39	49.4	3.89995
39	38.0	3.637586
48	28.7	3.356897
48	27.1	3.299534



Regression Output:

Constant	4.843
Std Err of Y Est	0.226
R Squared	0.810
No. of Observations	12
Degrees of Freedom	10
X Coefficient(s)	-0.02714
Std Err of Coef.	0.004153

half-life 25.5 hours

AR = Applied Radioactivity
Linear regression analysis performed using Corel Quattro Pro 8 program.
Results (% AR) from pp. 42-47 of the study report.

Determination of Standard Deviation for Volatiles and Material Balances

	CO_2			Other Volatiles			Material Balances		
Hour	% AR	Mean	s.d.	% AR	Mean	s.d.	% AR	Mean	s.d.
Irradiated									
0	NA			NA			102.40		
0	NA			NA			102.28	102.3	0.06
15	0.00			0.00			99.06		
15	0.00	0.00	0.000	0.00	0.000	0.000	99.77	99.4	0.36
24	0.01			0.01			99.71		
24	0.01	0.01	0.000	0.01	0.010	0.000	99.60	99.7	0.05
31	0.01			0.00			96.82		
31	0.03	0.02	0.010	0.01	0.005	0.005	98.92	97.9	1.05
39	0.04			0.00			95.76		
39	0.06	0.05	0.010	0.00	0.000	0.000	95.51	95.6	0.12
48	0.08			0.00			94.52		
48	0.08	0.08	0.000	0.01	0.005	0.005	92.90	93.7	0.81
Dark Control									
48	NA			NA			102.32		
48	NA			NA			101.40	101.9	0.46

Results (% AR) from pp. 40, 41 of the study report.
Means calculated using Corel Quattro Pro 8 program equation @avg(A1..A2).
Standard deviations calculated using Corel Quattro Pro 8 program equation @std(A1..A2).

Fenamidone Photolysis in pH 7 Buffer Solution
MRID 45385830

Determination of Standard Deviation

	Fenamidone			RPA408056			RPA405862			Photo-H		
Hour	% AR	Mean	s.d.	% AR	Mean	s.d.	% AR	Mean	s.d.	% AR	Mean	s.d.
Irradiated												
0	101.0			0.7			0.6			0.0		
0	101.0	101.0	0.00	1.1	0.9	0.20	0.2	0.4	0.20	0.0	0.0	0.00
15	92.9			2.8			1.6			0.2		
15	91.0	92.0	0.95	4.7	3.8	0.95	1.9	1.8	0.15	0.4	0.3	0.10
24	87.3			7.1			2.2			1.0		
24	87.6	87.5	0.15	6.1	6.6	0.50	2.1	2.2	0.05	1.0	1.0	0.00
31	74.1			13.6			3.8			2.2		
31	48.1	61.1	13.00	27.7	20.7	7.05	10.0	6.9	3.10	4.8	3.5	1.30
39	49.4			26.4			7.9			3.8		
39	38.0	43.7	5.70	30.9	28.7	2.25	10.7	9.3	1.40	5.2	4.5	0.70
48	28.7			37.1			13.1			5.7		
48	27.1	27.9	0.80	34.1	35.6	1.50	13.6	13.4	0.25	5.3	5.5	0.20
Dark Control												
48	100.5			0.8			0.5			0.0		
48	99.6	100.1	0.45	1.0	0.9	0.10	0.7	0.6	0.10	0.0	0.0	0.00

Results (% AR) from pp. 42-48 of the study report.

Total Unidentified [^{14}C]Residues in Test Solutions

	Rec in Soln	Fen	RPA-408056	RPA-405862	Photo-H	Total Unidentified [^{14}C]		
Hour	% AR	% AR	% AR	% AR	% AR	% AR	Mean	s.d.
Irradiated								
0	102.40	101.0	0.7	0.6	0.0	0.10		
0	102.28	101.0	1.1	0.2	0.0	-0.02	0.04	0.06
15	99.06	92.9	2.8	1.6	0.2	1.56		
15	99.77	91.0	4.7	1.9	0.4	1.77	1.66	0.10
24	99.69	87.3	7.1	2.2	1.0	2.09		
24	99.58	87.6	6.1	2.1	1.0	2.78	2.44	0.35
31	96.81	74.1	13.6	3.8	2.2	3.11		
31	98.88	48.1	27.7	10.0	4.8	8.28	5.70	2.58
39	95.72	49.4	26.4	7.9	3.8	8.22		
39	95.45	38.0	30.9	10.7	5.2	10.65	9.44	1.22
48	94.44	28.7	37.1	13.1	5.7	9.84		
48	92.81	27.1	34.1	13.6	5.3	12.71	11.28	1.44
Dark Control								
48	102.32	100.5	0.8	0.5	0.0	0.52		
48	101.40	99.6	1.0	0.7	0.0	0.10	0.31	0.21

Results (% AR) from pp. 41-48 of the study report.

Means calculated using Corel Quattro Pro 8 program equation @avg(A1..A2).
Standard deviations calculated using Corel Quattro Pro 8 program equation @std(A1..A2).
Total Unidentified [14C] caculated by subtracting % AR Fenamidone + RPA408056 + RPA405832 + Photo H from total Rec in Soln.
example irrad. 48-hour rep B: 92.81% - 27.1 - 34.1 - 13.6 - 5.3 = 12.71%.

Attachment 2

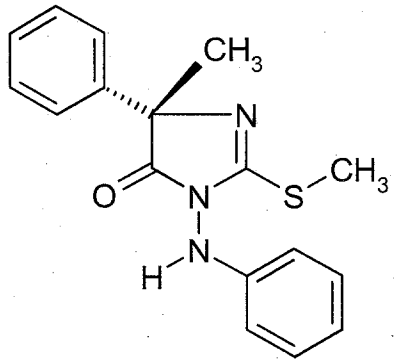
Structures of Parent and Transformation Products

RPA 407213

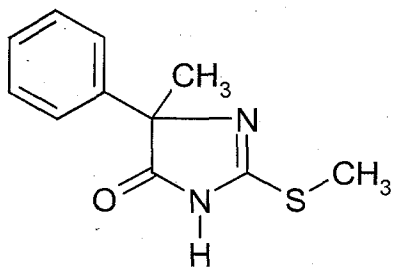
IUPAC name: (*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (S)-

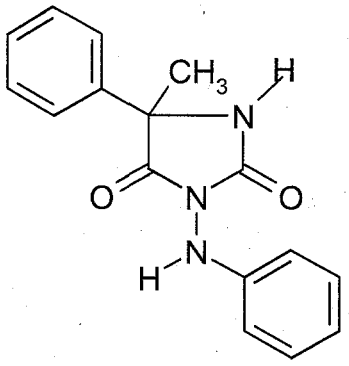
CAS #: 161326-34-7



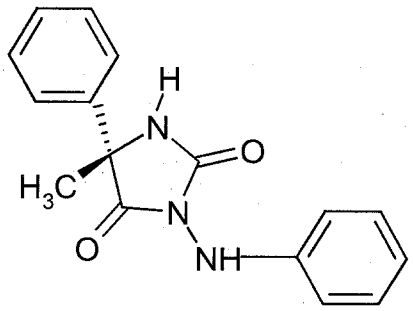
RPA 408056
IUPAC name: 5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one
CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-
CAS #: N/A



RPA 405862
IUPAC name: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-
CAS #: 153969-11-0



RPA 410193
IUPAC name: (S)-4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione
CAS name: N/A
CAS #: N/A

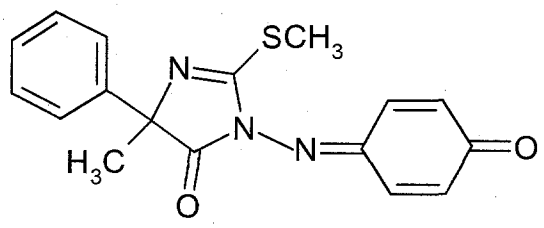


RPA 418915

IUPAC name: (*S*)-5-Methyl-2-methylthio-3-[4-oxo-2,5-cyclohexadien-1-ylidene)amino]-5-phenyl-3,5-dihydroimidazol-4-one

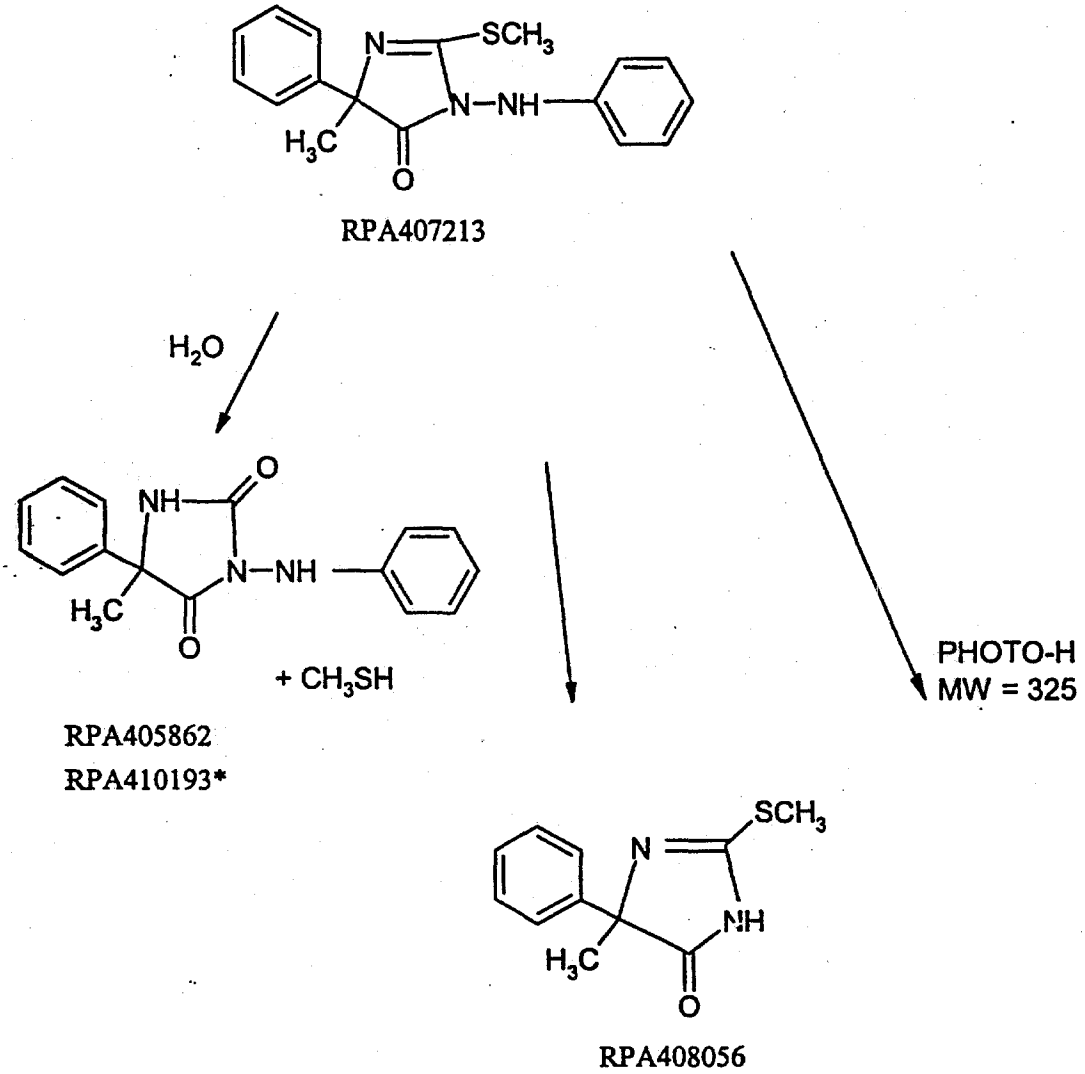
CAS name: N/A

CAS #: N/A



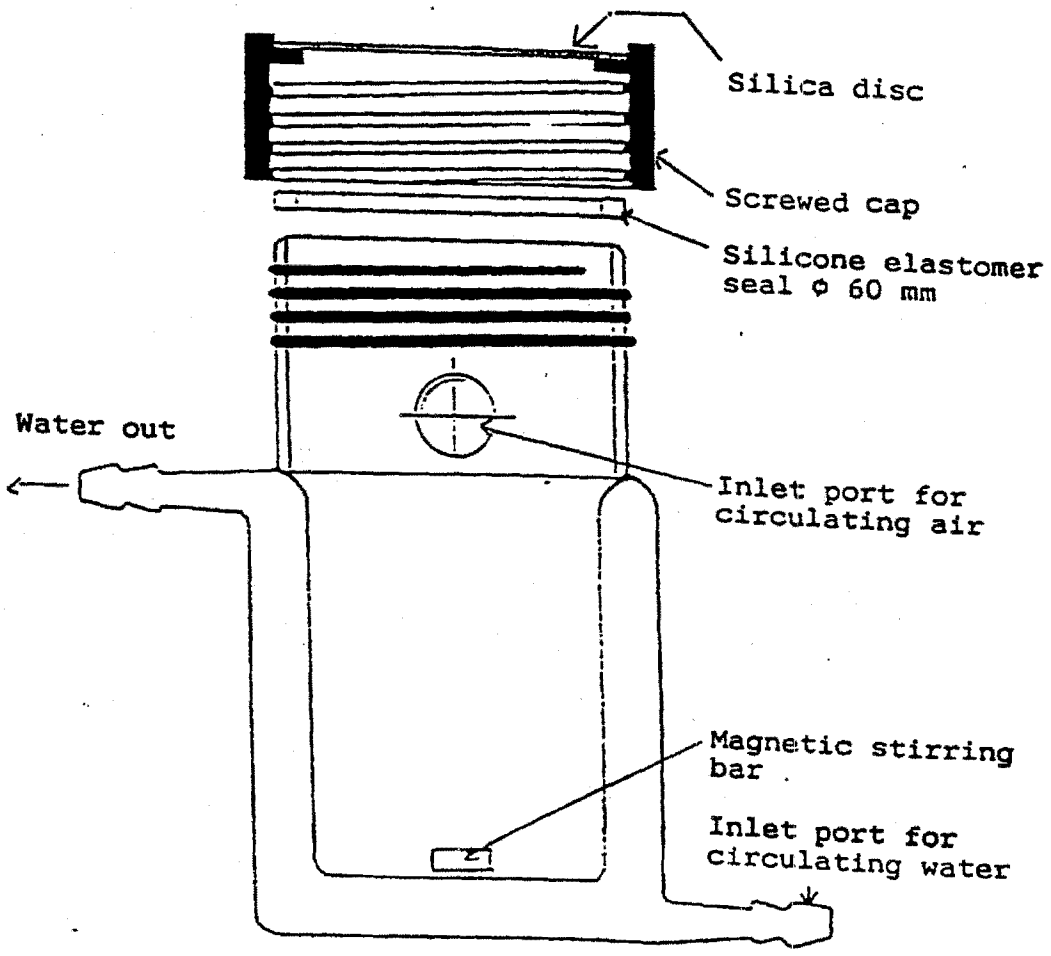
Attachment 3

Transformation Pathway Presented by Registrant
Illustration of Test System
Artificial Light Irradiation Spectrum

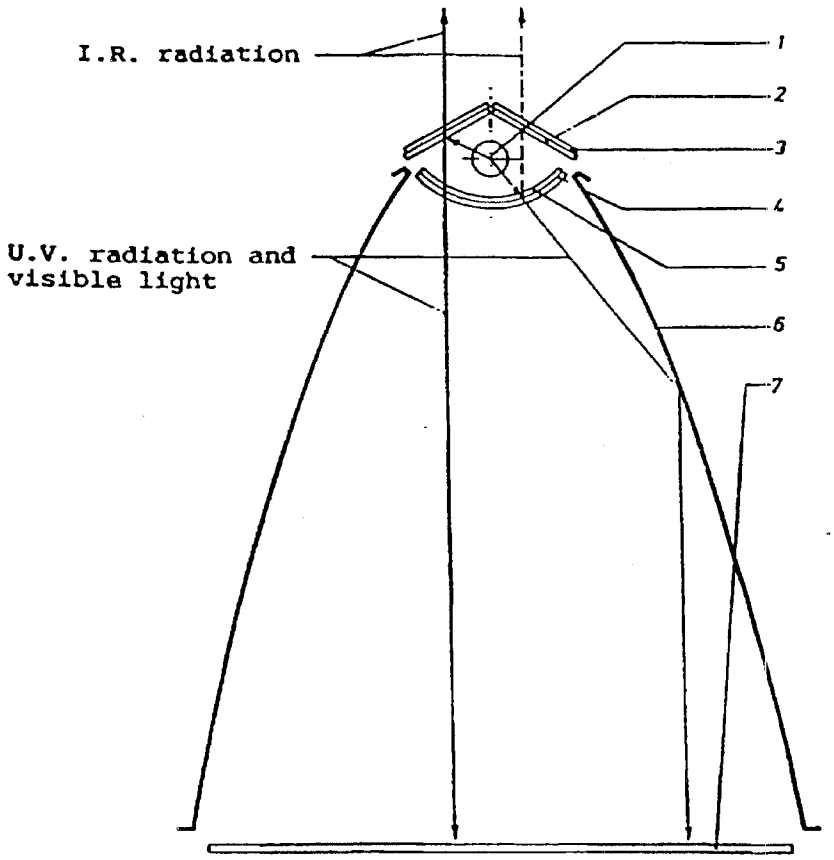


* : RPA410193 is the enantiomeric form, corresponding to RPA407213, of the racemic RPA 405862.

Figure 1: Photochemical reactor (internal diameter: 5.2 cm)

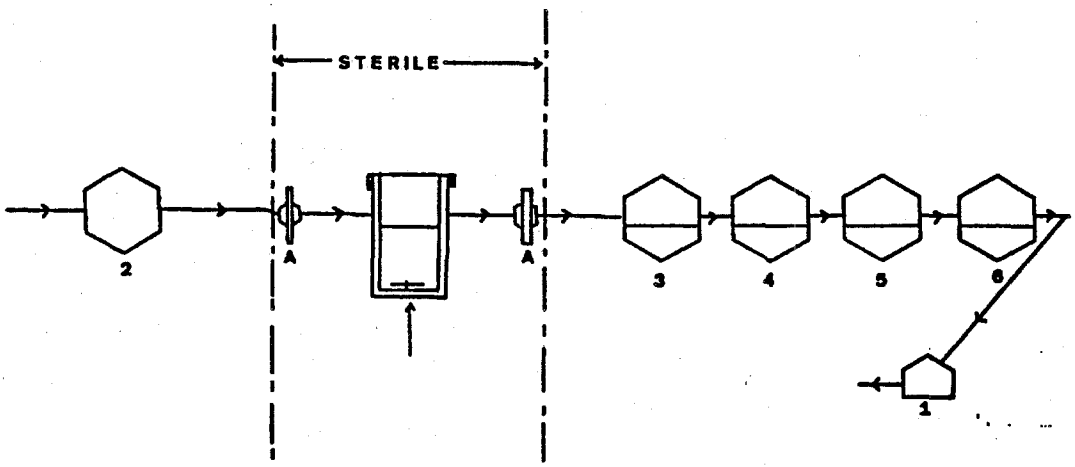


Appendix C1: Schematic diagram of Suntest



1 : Xenon lamp
2 : U.V. mirror
3 : Vis mirror
4 : I.R. Reflexion mirror
5 : Special U.V. filter
6 : Reflector
7 : Table

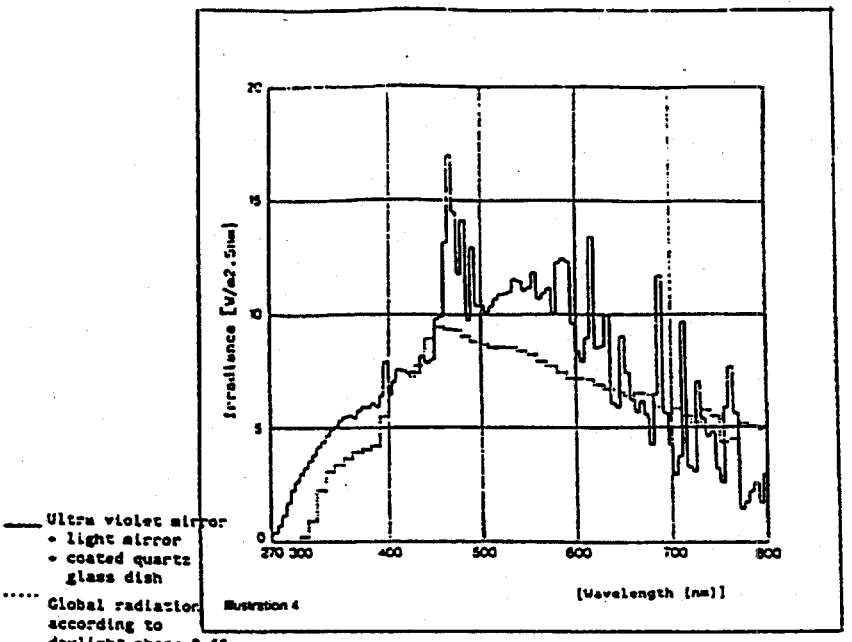
Figure 2: Scheme of the photodegradation set-up

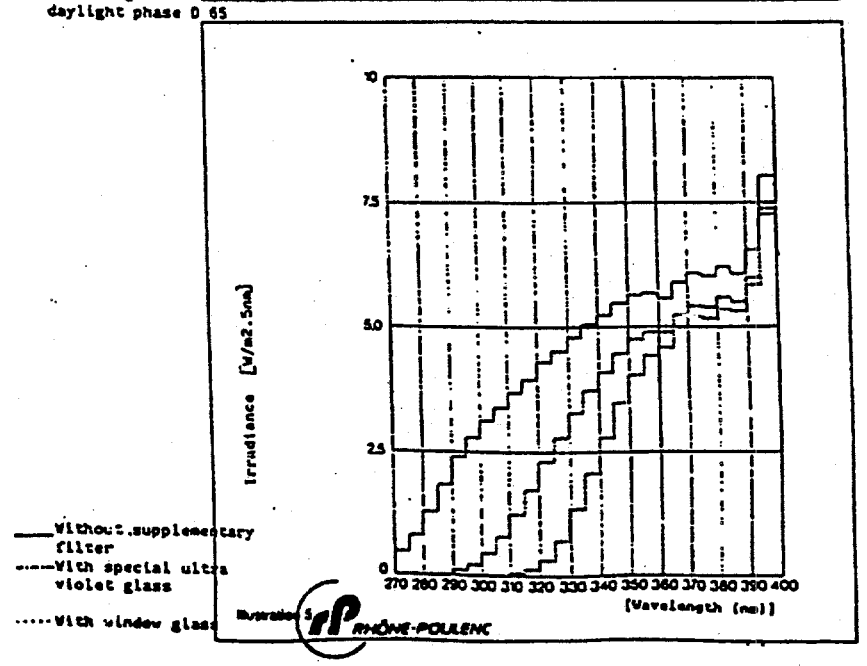


1. Pump KNF-Neuberger
2. Guard (before photoreactor)
3. Ethylene glycol monomethyl ether (EGME)
4. 2N Sodium hydroxide solution (A)
5. 2N Sodium hydroxide solution (B)
6. Water (before pump)

A. MILLEX FG50 0.2µm Filter Unit (50mm)
Autoclavable-Sterile

Appendix C2: Spectral energy distribution of the Xenon source





Appendix C2: Spectral energy distribution of the Xenon source